Pharmacologie médicale

Pharmaco-épidémiologie
CIC Bordeaux CIC1401

Bordeaux BPE PharmacoEpi

Cardiovascular risk associated with OTC-Strength Ibuprofen and paracetamol

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Introduction

- No clinical trials of paracetamol or low-dose ibuprofen with the power to study cardiovascular events
  - The PAIN study: RCT comparing directly paracetamol and ibuprofen (<1200mg) in adults for common acute painful episodes, 3000 subjects each arm, avg. 5 days, 20 tabs: no cardiovascular event
- Very little dose-response information or timing of events information in clinical trials
- Duration of treatment in clinical trials ≥ 4 week: much longer than real-life OTC use (3-5 days)
- Most observational studies: prescribed ibuprofen/ paracetamol use (Indication, dosage, duration, population characteristics are different from OTC users)

Method

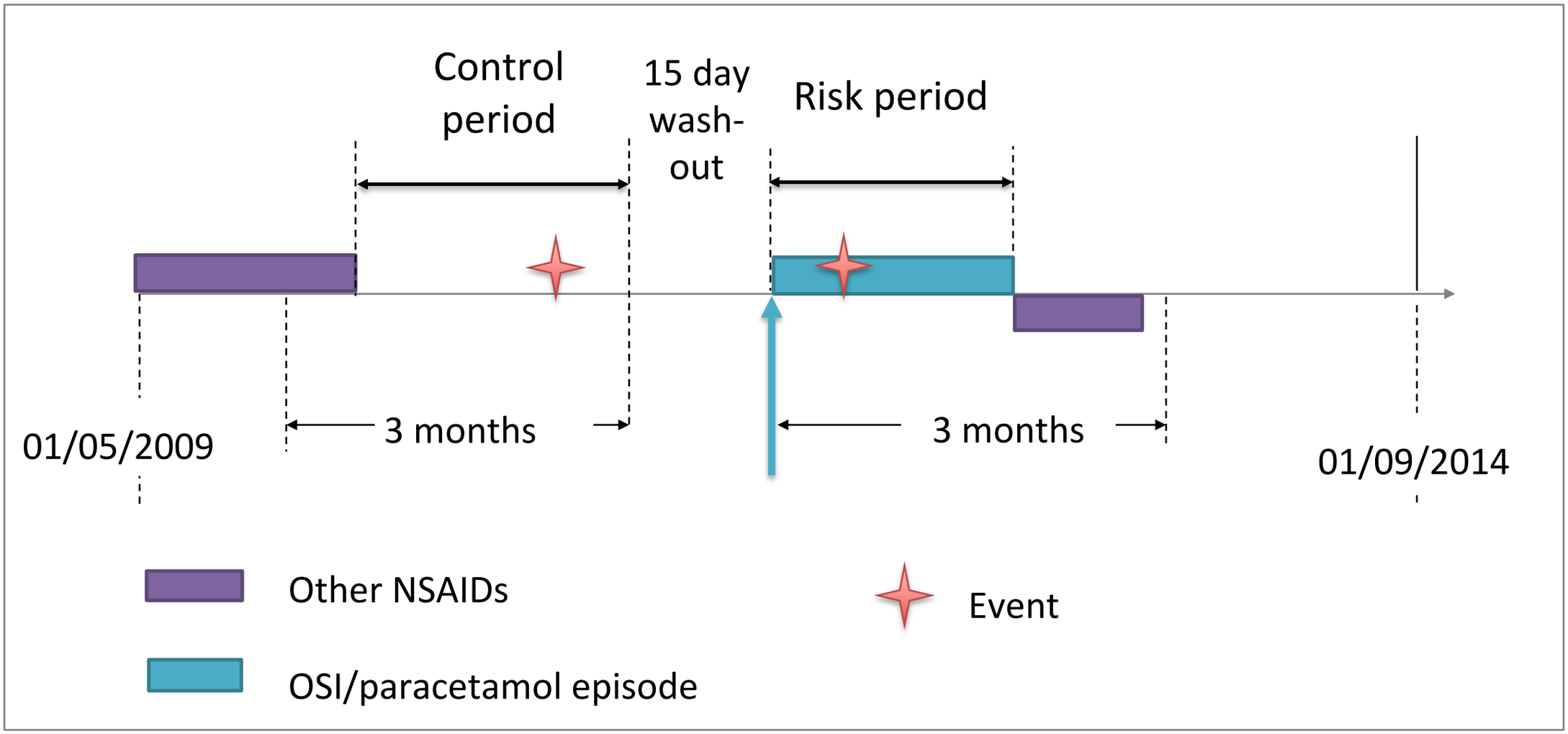
- **Data source:** EGB (*Échantillon généraliste des bénéficiaires*), 1/97 random permanent sample of the French healthcare database (see Poster
  - ~84% paracetamol use and ~70% ibuprofen use
  - Demographics data and hospital discharge diagnosis
- **Study design:**
  - Self-controlled cohort studies (SCC)
  - Propensity score matched study (PS-matched)
- **Participants:** Treatment episodes of OTC-strength ibuprofen (OSI) and paracetamol in adults between 2009-2014
- **Outcomes:**
  - Acute coronary syndrome (ICD-10 codes I21 and I20.0)
  - All-cause death

Method

- **Statistical analysis:**
  - Self-controlled cohort studies:
    - Event rate ratio (IRR) and 95% CI by conditional Poisson regression
    - Risk assessment in sub-groups: low-dose aspirin users and nonusers (Test of interaction for homogeneity of effect)
  - PS-matched study:
    - Paracetamol and OSI treatment episodes matched by PS greedy matching method (ratio 1:2, calipers 0.2 SD of logit PS)
    - Hazard ratios (HRs) and 95% CI by proportional hazards models (Gray and Fine method for competing risk)
    - Risk assessment in 15 days intervals
    - Risk assessment in sub-groups: low-dose aspirin users and nonusers

Method

- Self-controlled cohort:



OSI: OTC-strength ibuprofen

Results
Self-controlled cohort studies

Characteristics of Paracetamol and OSI episodes of use

	Paracetamol episodes N=1 025 877 (342 494 subjects)		OSI episodes n = 316 265 (168 407 users)	
Mean age, years (±SD)	**51.0**	**(20.3)**	**43.5**	**(16.0)**
<60 year-old	656160	(64.0)	262385	(83.0)
≥60 year-old	369717	(36.0)	53880	(17.0)
Female, n (%)	628570	(61.3)	198238	(62.7)
Prevalent long-term illnesses, n (%)				
Diabetes type I, II	62354	(6.1)	10640	(3.4)
Severe arterial hypertension	40344	(3.9)	4314	(1.4)
Coronary artery diseases	29681	(2.9)	2994	(0.9)
Concomitant low-dose aspirin , n (%)	**54878**	**(5.3)**	**11132**	**(3.5)**
Other concomitant drugs				
Anti-thrombotic agents	51985	(5.1)	6042	(1.9)
Serum lipid reducing agents	125780	(12.3)	13218	(4.2)

OSI: OTC-strength ibuprofen

Results
Self-controlled cohort studies

Risk of ACS associated with OSI dispensing

	Episodes (%)	Control period			Risk period			IRR (95%CI)
		Person-months	Event	IR¶	Person-months	Event	IR¶	
OSI								
All episodes	100.0	835119	70	0.84	853762	104	1.22	1.45 (1.07 – 1.97)¥
With low-dose aspirin	3.5	28805	54	18.7	29786	84	28.2	1.50 (1.07 – 2.12)
Without low-dose aspirin	96.5	806314	16	0.20	823976	20	0.24	1.22 (0.63 – 2.36)
Paracetamol								
All episodes	100.0	4002110	1133	2.83	4404210	1211	2.75	0.97 (0.90 – 1.05)
With low-dose aspirin	10.0	391210	951	24.3	449123	930	20.7	0.85 (0.78 – 0.93)
Without low-dose aspirin	90.0	3610900	182	0.50	3955086	281	0.71	1.41 (1.17 – 1.70)

OSI: OTC-Strength Ibuprofen;¶ Incidence rate per 10 000 person-months;

¥ No significant difference of risk between low-dose aspirin users and nonusers was found.

Results
Propensity score matched study

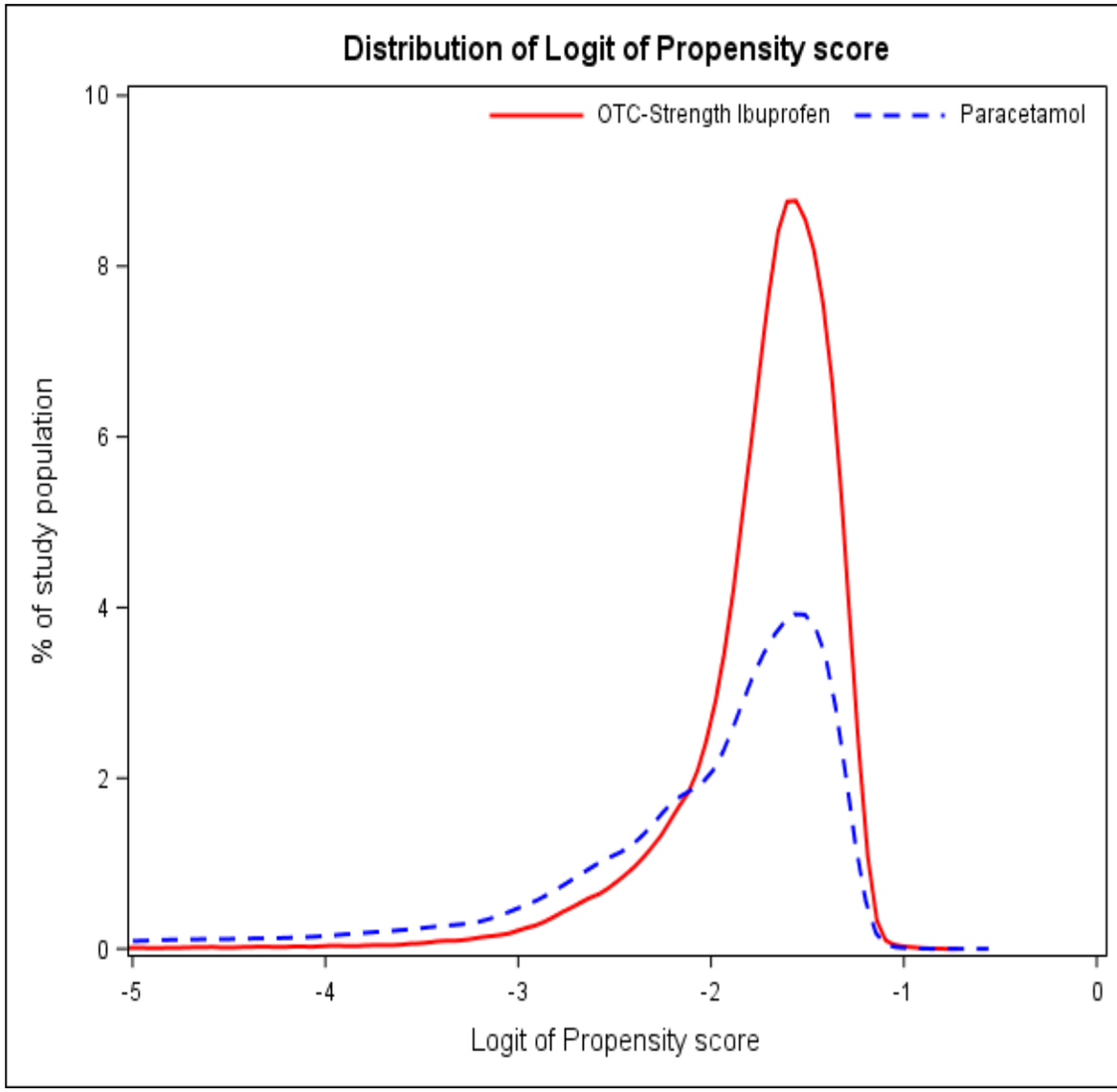
Characteristics of patient before and after matching by propensity score

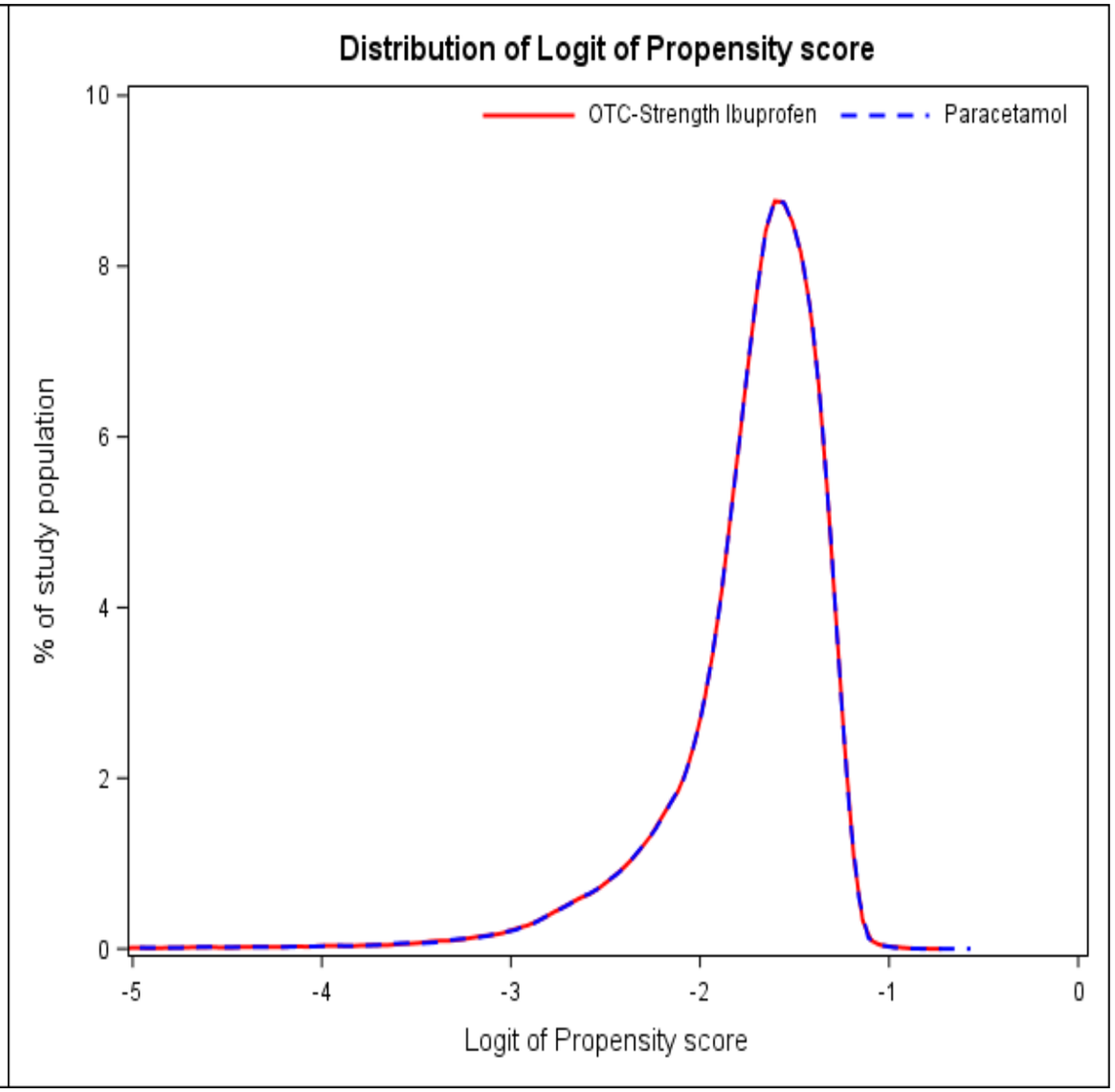
	Before matching		After matching		
	Paracetamol n = 1 368 664	OSI n = 209 566	Paracetamol n = 416 958	OSI n = 208 518	Standardized difference (%)
Mean age, years (±SD)	51.8 (19.4)	44.5 (16.1)	44.5 (16.1)	44.5 (16.1)	0.00
Female, (%)	62.0	63.9	63.9)	63.9	0.00
Prevalent long-term illnesses, (%)					
Diabetes type I, II	6.3	3.5	3.7	3.5	-0.97
Severe arterial hypertension	3.6	1.4	1.4	1.4	0.34
Drug use in the 3 preceding months, n (%)					
Antithrombotic agents	10.8	4.3	4.2	4.3	0.55
Serum lipid reducing agents	15.9	9.7	9.4	9.6	0.44

OSI: OTC-Strength Ibuprofen

Results

Propensity score matched study





Results
Propensity score matched study

Risk of acute coronary syndrome associated with OSI (vs.Paracetamol)

	Paracetamol (ref.)			OSI			
	Person-months	Events	IR¶	Person-months	Events	IR¶	Hazard ratio (95%CI)
Day 1-15	330304	47	1.42	165690	40	2.41	1.70 (1.11 – 2.59)
Day 16-30	298129	41	1.29	150162	8	0.50	0.40 (0.19 – 0.85)
Month 1	628410	88	1.40	315831	48	1.52	1.10 (0.77 – 1.56)
Month 2	567248	51	0.90	292522	28	0.96	1.07 (0.67 – 1.71)
Month 3	472362	64	1.35	261603	22	0.84	0.62 (0.38 – 1.01)
All follow-up	1631516	203	1.24	851037	98	1.15	0.94 (0.74 – 1.20)

OSI: OTC-Strength Ibuprofen; ¶ Incidence rate per 10 000 person-months;

Results
Propensity score matched study

Risk of all-cause death associated with OSI (vs Paracetamol)

	Paracetamol (ref.)			OSI			
	Person-months	Events	IR¶	Person-months	Events	IR¶	Hazard ratio (95%CI)
Day 1-15	330318	92	2.78	165700	29	1.75	0.63 (0.41 – 0.95)
Day 16-30	318380	113	3.55	160341	40	2.49	0.70 (0.49 – 1.01)
Month 1	628458	205	3.26	315864	69	2.18	0.67 (0.51 – 0.88)
Month 2	567248	240	4.23	292522	76	2.60	0.61 (0.47 – 0.79)
Month 3	472393	191	4.04	261614	84	3.21	0.79 (0.61 – 1.03)
All follow-up	1610522	836	5.19	840535	327	3.89	0.75 (0.66 – 0.85)

OSI: OTC-Strength Ibuprofen; ¶ Incidence rate per 10 000 person-months

Results

Propensity score matched study

Risk of acute coronary syndrome associated with OSI (vs. Paracetamol) in low-dose aspirin users and nonusers

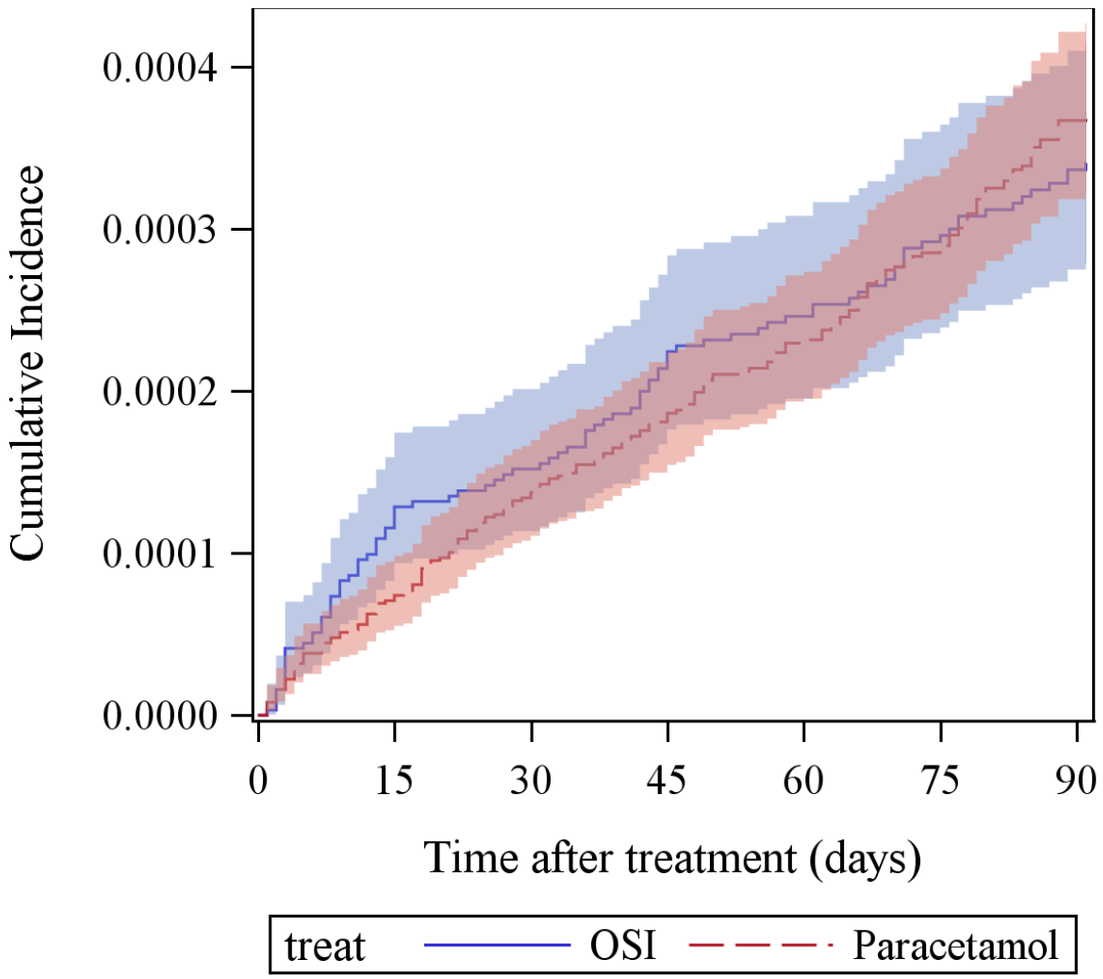
	Paracetamol (ref.)			OSI			
	Person-months	Events	IR¶	Person-months	Events	IR¶	Hazard ratio (95%CI)
With low-dose aspirin							
Day 1-15	11296	42	1.27	5640	39	2.35	1.85 (1.20 – 2.86)
Day 16-30	11041	41	1.29	5496	8	0.50	0.38 (0.18 – 0.81)
Month 1	21620	88	1.40	10770	48	1.52	1.09 (0.76 – 1.54)
All follow-up	56430	203	1.24	29167	98	1.15	0.93 (0.73 – 1.18)
Without low-dose aspirin							
Day 1-15	318043	11	0.34	159595	6	0.37	1.09 (0.40 – 2.94)
Day 16-30	306370	5	0.16	154407	3	0.19	1.19 (0.28 – 4.98)
Month 1	604924	16	0.26	304197	9	0.29	1.12 (0.50 – 2.53)
All follow-up	1570306	45	0.28	819571	20	0.24	0.85 (0.50 – 1.43)

OSI: OTC-Strength Ibuprofen; ¶ Incidence rate per 10 000 person-months

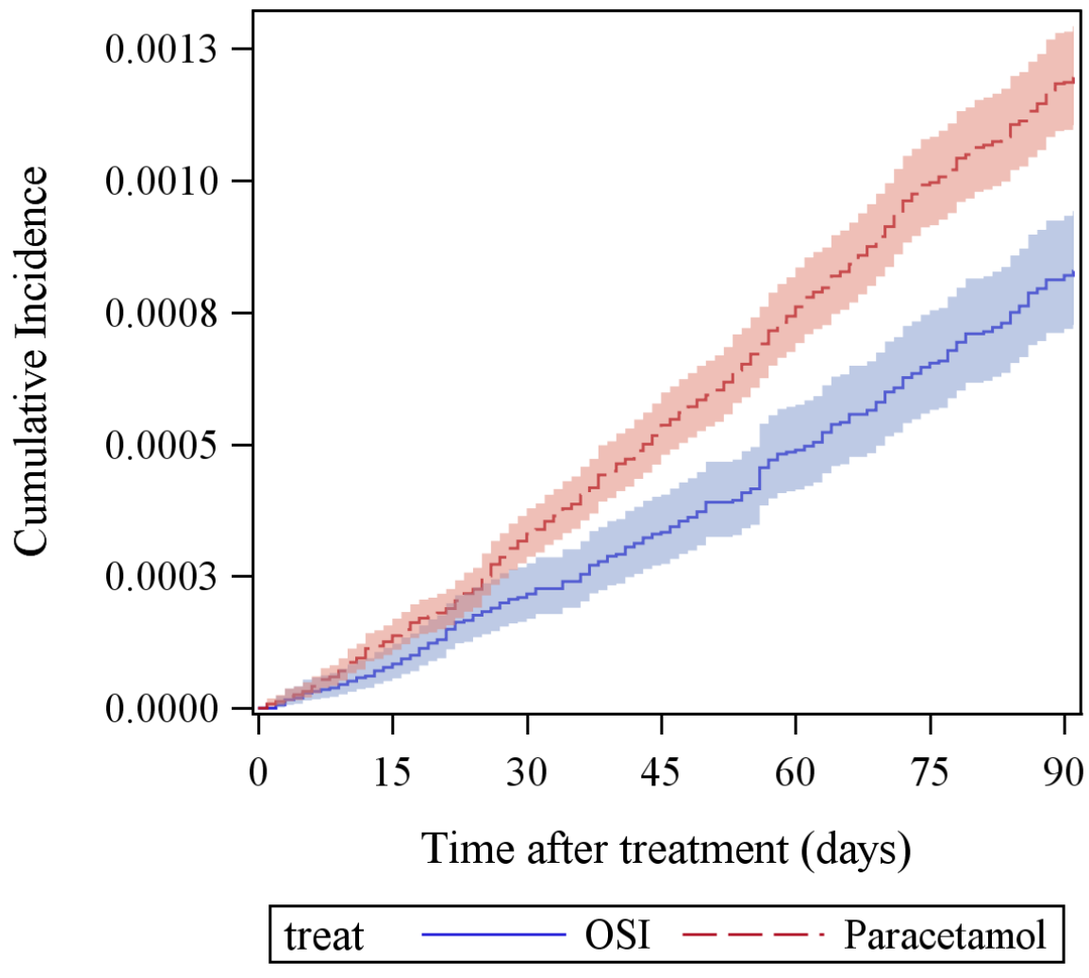
Results

Propensity score matched study

Acute coronary syndrome



All-cause death



Cumulative incidence of events with confidence limits.
P-value estimated by Gray's test for equality of cumulative incidence functions

Discussion and research perspective

Strengths and weaknesses

- Strengths
  - Database: covers most of paracetamol and ibuprofen use
  - Method: different methods complement each other
- Weaknesses
  - Small event number
  - Not ‘real’ OTC
  - Exposure misclassification bias

Research perspectives

Studies in the national claims database:

- A case-control study to verify the cardiovascular risk with OTC ibuprofen in older patients
- PS-matched cohort study to compare the risk of OSI and P in the elderly
- Compared with « neutral » drugs with similar indications (oral antibiotics, other non-COX painkillers)
- Extend to other outcomes (UGIB, renal failure)

General conclusions

- Relative risks consistent across studies
  - Ibuprofen (younger users)
    - Increase of ACS risk <15 days in low-dose aspirin users but no difference at 1 month
    - No increased risk in aspirin non-users compared to paracetamol
  - Paracetamol (older users)
    - Older users without low-dose aspirin use: not enough matched episodes to compare with Ibuprofen
    - Risk of death needs further study
- Absolute potential increase of risk is very small with OSI or paracetamol

Thank you for your attention

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and don't forget

Bordeaux PharmacoEpi festival

May 22-24, 2018

with

John Ioannidis

Susana Perez-Gutthann

Corinne deVries

Tom Walley

Munir Pirmohammed

And perhaps even Jacques LeLorier !!!